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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,731	12/15/2003	Eberhard Weihe	029310.52995US	6798

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EXAMINER	
STANDLEY, STEVEN H	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/734,731	WEIHE ET AL.	
	Examiner	Art Unit	
	Steven H. Standley	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *5,6 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 7-12, 14-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/05/2006 has been entered.

2. Claims 1-4, 7-12, and 14-15 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Objections/Rejections: Withdrawn

Claim Rejections - 35 USC § 112

3. Rejection of claims 1-4, 7-12, and 14-15 is withdrawn because Applicant deleted "stringent conditions."

4. Rejection of claims 2-4, and 7 is withdrawn because Applicant has defined in the claim what is meant by genetic engineering.

5. Rejection of claims 1-4, and 7 is withdrawn because Applicant has included a step wherein it is determined if the substance is pain regulating.

Claim Rejections - 35 USC § 102

6. Rejection of claims 1-4, 7-12, and 14 is withdrawn because Applicant added an additional active step to claim 1.

Objections/Rejections: Maintained/New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4, 7-12, and 14-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant has amended claim 1 to read, "or a protein encoded by a nucleic acid which is the ***reverse complement*** of a polynucleotide comprising SEA ID NO 1, 3, 5, etc." In other words, applicant is now claiming a polypeptide encoded by the non-coding strand. While there are examples of genes that encode different polypeptides on the coding strand and on the strand that is the reverse complement, *there is no basis in the specification, nor any indication of what the encoded polypeptide might be.*

8. Claims 1-4, 7-12, and 14-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant has amended claim 1, part (b) to read, "...ionic milieu..." There is no basis or definition in the specification for the term.

9. Rejection of claims 1-4, 7-12, and 14-15 under 35 USC § 112, 1st paragraph, enablement is maintained for the reasons made of record in the office action dated 6/14/05 and the reasons below. Applicant's arguments have been fully considered and not found to be persuasive. Applicant argues that the examiner is applying a heightened standard. The examiner disagrees and maintains the argument that the method is unlikely to find any compounds that are pain related. Applicant is enabled for a method of identifying substances that bind to full-length Vglut1, and then testing those substances in an animal model of pain, however applicant is not enabled for proteins 90% homologous or peptides more than 10 amino acids long or proteins that bind the protein that is reverse complement of the coding region of the nucleic acid encoding the protein. Further, applicant is not enabled for a method wherein measuring a "functional parameter results in detecting a substance that regulates pain. Applicant argues that BNPI need not cause pain, but merely play a functional role in it. However, enhanced expression of BNPI (also called Vglut1) may have nothing at all to do with pain.

Enhanced expression of BNPI in an animal model of pain is merely an invitation to do additional research. One would have to further experiment to determine if expression of BNPI is really linked to pain in any way. Additionally, further experimentation would also be required to determine if a compound should inhibit, activate, or otherwise modulate BNPI. In short, injection of Freund's adjuvant or collagen causes elevated expression of Vglut1 and induction of pain. That does not mean elevated Vglut1 causes pain.

5. Neither prior nor post-filing date art supports a role of vglut1 in mediating pain. For instance, analysis of expression by microarray of proteins with a greater than two-fold change in an animal model of pain did not find that vglut1 (BNPI) was elevated (Sun et al 2002). Sun et al identify more than 50 proteins that show greater than two-fold expression in an animal model of pain (see Table I, page 3). However, Vglut1 is not among them. Further, Sun et al are silent as to whether any of the proteins identified by their method are necessarily involved in pain. Sun et al explain that the study is merely a starting point for determining if one or more of the genes actually represent appropriate therapeutic targets by having a role in pain modulation, saying "The aim of this study was to find genes that are enriched in the dorsal spinal cord ***that can potentially play important roles*** in pain transmission, pain modulation, and pathophysiological conditions [page 7, right col; emphasis added]." Thus, the art does not recognize that mere upregulation in these circumstances is predictive of causality.

Applicant argues that the Examiner's interpretation of Sun et al is unreasonable because it requires that Sun et al teach every possible protein relevant to pain. The examiner disagrees. Sun et al find many proteins that are elevated in a pain model

(Vglut1 is not one of them), but Sun et al also indicate that that finding is just a starting point. Thus, not only does Sun et al not find the instant protein elevated, Sun et al say that even if it were, it would really mean it had a modulatory relationship to pain.

Applicant argues on page 8 of Remarks that there is nothing in the record to suggest any reason why the method would not work as claimed. In contrast to applicant's assertion, the entire prior rejection of 6/14/05 and 3/09/06 under 35 USC 112, 1st enablement, and the above arguments all describe why the method will not detect compounds that regulate pain, as well as various other aspects of the claims that are not enabled. Thus, while Jensen et al (cited below under 35 USC § 102(b)) use the method recited in the claims, they fail to find a compound that binds VGlut1 that mediates pain. Jensen et al find a compound (glutamate) that binds to AMPA, Kainate, NMDA, and mGluR receptors as well as a plethora of transporters unrelated to those currently claimed. Further, they find that NMDA receptors specifically mediate pain (see below).

Therefore, for the reasons given in the office action of 6/14/05 and 3/09/06 and the reasons given above, it would require undue experimentation for one skilled in the art to make or use the invention as currently claimed.

10. Rejection of claims 1-4, 7-12, and 14-15 under 35 USC § 112, 1st paragraph, written description is maintained for the reasons made of record in the office action dated 6/14/05 and 3/09/06. Applicant's arguments have been fully considered and not found to be persuasive. Applicant argues that the amendment of claim 1 overcomes the

rejection. The amendment to claim 1 includes a list of 'functional parameters' that includes measurement of regulation, inhibition, or activation of receptors, ion channels, or enzymes or via measurement of a modification in gene expression, ionic medium, pH or membrane potential, or via a modification in enzyme activity or concentration of second messenger.

However, neither the specification nor the art teach a relationship between Vglut1 and elements such as receptors, ion channels, enzymes, ionic medium, pH, enzyme activity or concentration of second messenger sufficiently for applicant to claim a generic 'measurement' of an enormous and varied genus of 'functional parameters' encompassed by the varied and unrelated things in the list above.

Further, applicant is claiming identifying compounds that bind to any polypeptide of 10 or more amino acids of that of SEQ ID NO: 4. However, applicant does not have written description of such variants to find molecules related to pain. The claims are drawn part polypeptides 10 or more amino acids in length of the polypeptides. The claims do not require that the polypeptides possess any particular biological activity except binding to a generic substance, nor any particular conserved structure, or other disclosed distinguishing feature. Therefore, there are no clear structural limitations on the complex of polypeptides claimed. Thus, the claims are drawn to a genus of polypeptides that constitute a complex that is defined only by 10 or more amino acids of the protein.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. In the instant

application, no such distinctions have The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to

be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only polypeptides comprising the amino acid sequence set forth in a SEQ ID NO: 4 but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

11. Rejection of claims 1-4, 7-12, and 14-15 under 35 USC 112, 2nd paragraph for failing to adequately redefine the term ""a method of detecting a pain-regulating substance," is maintained for reasons made of record in the office action of 6/14/05 and 3/09/06. Again, it is not clear what constitutes "***a potential*** regulating influence" in applicant's definition of the phrase "a method of detecting a pain-regulating substance. Applicant argues on page 10 of Remarks that a person of skill in the art would have no trouble in determining the scope of the claim. This is not found persuasive because the scope of the claim is not at issue. What is at issue is whether "a potential regulating influence" means the substance will, or will not be a pain-regulating substance.

12. Rejection of Claims 1-4, 7-12, and 14-15 under USC 112, 2nd paragraph for omitting essential steps is maintained for reasons made of record in the office action of 6/14/05 and 3/09/06.

13. Rejection of Claims 1-4, 7-12, and 14-15 under USC 112, 2nd paragraph for being indefinite because the relationship between the step a and step b is unclear is maintained for reasons made of record in the office action of 6/14/05 and 3/09/06. Again, step (b) reads "measuring the binding of the test substance to the protein or part protein synthesized by the cell," it does not say 'measuring the binding of the test substance to the protein or part protein, or to the protein or part protein synthesized by the cell.' Instead, it actually indicates that the test substance is only to be tested on a protein synthesized by the cell if it is a "part protein." Further step (b) does not measure the binding of a test substance incubated with the extraneous "or a cell" mentioned in the third from the last line (on the right) in step (a).

14. Rejection of Claims 1-4, 7-12, and 14-15 under USC 112, 2nd paragraph for using the term 'functional parameter,' without adequately defining it is maintained for reasons made of record in the office action of 6/14/05 and 3/09/06. It is unclear how measuring pH or ionic milieu is measuring a functional parameter of Vglut1. A parameter is a limit or boundary that can be varied in an experiment, not a dependent variable. However, it is unclear what definition Applicant is giving it because the claim recites things that can be measured or controlled and varied. It is unclear how measuring ionic milieu (which is something the experimenter can control) helps identify a substance that is pain-regulating.

15. Claims 1-4, 7-12, and 14-15 are rejected because it is not clear whether the final step is a further step of testing the compound in an animal model, or whether the

determination is being made simply after testing a "functional parameter," and concluding that it is pain regulating.

16. Rejection of Claims 4 under USC 112, 2nd paragraph for reciting expression of a form of G-protein without any clear relationship between it and the invention is maintained for reasons made of record in the action of 6/14/05 and 3/09/06.

17. Claims 1-5, 7-12, and 14-15 are further rejected under 35 USC § 112, 2nd paragraph for reciting 'ionic milieu.' It is not clear what the claim intends to measure when it recites 'ionic milieu.' The specification gives no clear rendering of the definition, nor is it clear to one of skill in the art what "measuring....ionic milieu" means.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1, 10-12, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Jensen et al (1992).

Jensen et al teach intracerebral injection of glutamate into the brain stem and medulla and observing pain responses from rats (see abstract, Jensen). Glutamate is known to bind BNPI (see below), and vGlut1 is known to be in the brainstem and medulla. Jensen et al meets the limitations of claim 1 because Jensen has brought glutamate (a pain-regulating substance) into contact with GNPI (see below), measured

a "functional parameter (this could simply be measuring the glutamate concentration injected or it could be the behavior)," and determined that glutamate causes pain (see Figure 4, Jensen et al, for instance). Further, Jensen et al show that the pain response is blocked by NMDA receptor antagonists (see Figure 4), which constitutes measuring receptors or ionic milieu of claims 10-12. Jensen et al also uses labeled ligand which can be displaced by endogenous glutamate, meeting the limitations of claim 10. Finally, Jensen et al measure neuropathic pain by measuring vocalization and vigorous escape behavior, this meeting the limitations of claim 14. It is also of note that Jensen et al show that NMDA receptors, not Vglut1 transporters, mediates neuropathic pain.

Conclusion

19. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Bellocchio et al show that glutamate binds to the Vglut1 transporter and is transported (see figure 1). Li et al show that Vglut1 is present in the medulla (see abstract).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven H. Standley whose telephone number is (571) 272-3432. The examiner can normally be reached on 8:00-4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Janet Andre can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Steven Standley, Ph.D.

11/26/06

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